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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/627,206	07/27/2000	Jane A. Gross	98-75C2	1238

7590 05/23/2005

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EXAMINER	
ZEMAN, ROBERT A	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/627,206	GROSS, JANE A.	
	Examiner	Art Unit	
	Robert A. Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *89 and 102-111* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *89 and 102-111* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

S.O.O.

DETAILED ACTION

The response filed on 2-10-2005 is acknowledged. Claims 89 and 102-111 are pending and currently under examination.

Claim Rejections Maintained

35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The rejection of claims 89, 102-103, 105-108 and 110-111 under 35 U.S.C. 102(a) as being anticipated by Bram et al. (WO 98/39361) is maintained for the reasons of record.

Applicant argue:

1. Bram et al. presents no data showing how a construct such as those described in the present application can be made. or any data demonstrating that said construct would work to inhibit B cell activity.

2. Bram et al. does not show specifically describe all the receptors of the present claims or identify ztnf4 or any other ligand.

3. Bram et al. does not provide data showing that the extracellular domain of any ztnf4 receptor will maintain its ability to bind ztnf4 absent the transmembrane and intracellular domains of the receptor.

4. Bram et al. does not show that the extracellular domain of TACI will bind to any ligand, let alone ztnf4 when fused to an Fc domain of an antibody.

5. Bram et al. does not teach what particular kinds of Fc fragments may be used in the fusion.

6. Bram et al. cannot properly inherently anticipate the claimed subject matter because Bram et al. does not teach the group of soluble receptors encompassed by the instant claims or does it disclose ztnf4 as a ligand for the receptors. Bram et al. does nothing more than assume that a ligand exists for this receptor and such an assumption is not a proper basis for a finding of anticipation.

7. Bram et al. disclose that the role of the ligand for inhibiting lymphocyte proliferation, the identity of the TACI protein is unknown and under law this admitted likelihood cannot serve as basis for inherent anticipation (*In re Rijckaert)*.

Applicant's arguments have been fully considered and deemed non-persuasive.

The instant claims are drawn to methods of inhibiting B cell proliferation by the administration of a soluble form a ztnf4 receptor (TACI) wherein said receptor binds ztnf4. Said soluble form of the ztnf4 receptor can comprise the extracellular domain of the TACI protein and may be optionally fused to the heavy chain constant region of human immunoglobulins. Additionally, said soluble form of the ztnf4 receptor may comprise multiple polypeptide fusions.

Ztnf4 is a member of the tumor necrosis factor (TNF) superfamily. Ztnf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Ztnf4 is a ligand for TACI and is also known in the art as BLyS, neutrokine α, BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see page 24, lines 24-26). Moreover, Bram et al. disclose that the "subunits" of the construct (i.e. TACI and the Fc domain of the Ig) can be linked by peptide bonds (see page 20, line 1). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular domain (see page 18, lines 27-30). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity (see page 8, lines 1-6). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit the activity of ztnf4, even though its identity is not known, since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. Hence, Applicant's argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that said composition binds ztnf4. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant

invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand).

Additionally Applicant is reminded "the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best 562* F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Moreover, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 105-106 and 110-111, Bram et al. anticipates this limitation since their disclosed fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Finally, with regard to Applicant's argument that case law (*In re Rijckaert)* states that an admitted likelihood cannot serve as a basis for inherent anticipation, Applicant is reminded that *In re Rijckaert* deals a fact pattern that is not analogous with the instant case. *In re Rijckaert* deals with differing mechanical devices, whether structural features are present and the applicability of unknown facts in the formation of an obviousness rejection. In the instant case there is no doubt as to whether an unknown characteristic would be present since the compositions are the same. Moreover, contrary to Applicant's assertion to the contrary, *In re Rijckaert* states "[t]hat which may be inherent is not necessarily known". Consequently, for the reasons set forth above, Bram et al. anticipates all the limitations of the rejected claims.

The rejection of claims 89, 102-103, 105-108 and 110-111 are rejected under 35 U.S.C. 102(e) as being anticipated by Bram et al. (U.S. Patent 5,969,102 – IDS-5) is maintained for reasons of record.

Applicant argue:

1. Bram et al. presents no data showing how a construct such as those described in the present application can be made. or any data demonstrating that said construct would work to inhibit B cell activity.

2. Bram et al. does not show specifically describe all the receptors of the present claims or identify ztnf4 or any other ligand.

3. Bram et al. does not provide data showing that the extracellular domain of any ztnf4 receptor will maintain its ability to bind ztnf4 absent the transmembrane and intracellular domains of the receptor.

4. Bram et al. does not show that the extracellular domain of TACI will bind to any ligand, let alone ztnf4 when fused to an Fc domain of an antibody.

5. Bram et al. does not teach what particular kinds of Fc fragments may be used in the fusion.

6. Bram et al. cannot properly inherently anticipate the claimed subject matter because Bram et al. does not teach the group of soluble receptors encompassed by the instant claims or does it disclose ztnf4 as a ligand for the receptors. Bram et al. does nothing more than assume that a ligand exists for this receptor and such an assumption is not a proper basis for a finding of anticipation.

7. Bram et al. disclose that the role of the ligand for inhibiting lymphocyte proliferation, the identity of the TACI protein is unknown and under law this admitted likelihood cannot serve as basis for inherent anticipation (*In re Rijckaert)*.

8. Only the claimed subject matter and not every statement set out in the '102 patent is presumed to be valid under 35 U.S.C. 282. Because the '102 patent does not claim the method of the present invention, such statements are not entitled to presumptions of validity especially since the reference only speaks in terms of likelihood of a claimed result.
Applicant's arguments have been fully considered and deemed non-persuasive.

The instant claims are drawn to methods of inhibiting B cell proliferation by the administration of a soluble form a ztnf4 receptor (TACI) wherein said receptor binds ztnf4. Said soluble form of the ztnf4 receptor can comprise the extracellular domain of the TACI protein and may be optionally fused to the heavy chain constant region of human immunoglobulins. Additionally, said soluble form of the ztnf4 receptor may comprise multiple polypeptide fusions.

Ztnf4 is a member of the tumor necrosis factor (TNF) superfamily. Ztnf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Ztnf4 is a ligand for TACI and is also known in the art as BLyS, neutrokine α, BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see column 17, lines 16-18). Moreover, Bram et al. disclose that the "subunits" of the construct (i.e. TACI and the Fc domain of the

Ig) can be linked by peptide bonds (see column 13, line 64). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular domain (see column 13, lines 7-12). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity (see column 5 lines 45-53). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit the activity of ztnf4, even though its identity is not known, since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. Hence, Applicant's argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that said composition binds ztnf4. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand).

Additionally, Applicant is reminded "the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best 562* F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977).

Moreover, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 105-106 and 110-111, Bram et al. anticipates this limitation since their

disclosed fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Finally, with regard to Applicant's argument that case law (*In re Rijckaert)* states that an admitted likelihood cannot serve as a basis for inherent anticipation, Applicant is reminded that *In re Rijckaert* deals a fact pattern that is not analogous with the instant case. *In re Rijckaert* deals with differing mechanical devices, whether structural features are present and the applicability of unknown facts in the formation of an obviousness rejection. In the instant case there is no doubt as to whether an unknown characteristic would be present since the compositions are the same. Moreover, contrary to Applicant's assertion to the contrary, *In re Rijckaert* states "[t]hat which may be inherent is not necessarily known". Additionally, with regard to Applicant's assertion that only the claimed subject matter and not every statement set out in the '102 patent is presumed to be valid under 35 U.S.C. 282 the MPEP states:

"The use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain." *In re Heck*, 699 F.2d 1331, 1332-33, 216 USPQ 1038, 1039 (Fed. Cir. 1983) (quoting *In re Lemelson*, 397 F.2d 1006, 1009, 158 USPQ 275, 277 (CCPA 1968)).

Consequently, for the reasons set forth above, Bram et al. anticipates all the limitations of the rejected claims.

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The instant claims are drawn to methods of inhibiting B cell proliferation by the administration of a soluble form of a ztnf4 receptor (TACI). Said soluble form of the ztnf4 receptor can comprise the extracellular domain of the TACI protein that is optionally fused to the heavy chain constant region of human immunoglobulins. Additionally, said soluble form of the ztnf4 receptor may comprise multiple polypeptide fusions.

The rejection of claims 89 and 102-111 under 35 U.S.C. 103(a) as being unpatentable over Bram et al. (WO 98/39361 – IDS-5), as cited above, in view of Presta et al. (U.S. Patent 5,739,277) is maintained for reasons of record.

Applicant argues:

1. Bram et al. presents no data showing how a construct such as those described in the present application can be made. or any data demonstrating that said construct would work to inhibit B cell activity.

2. Bram et al. does not show specifically describe all the receptors of the present claims or identify ztnf4 or any other ligand.

3. Bram et al. does not provide data showing that the extracellular domain of any ztnf4 receptor will maintain its ability to bind ztnf4 absent the transmembrane and intracellular domains of the receptor.

4. Bram et al. does not show that the extracellular domain of TACI will bind to any ligand, let alone ztnf4 when fused to an Fc domain of an antibody.

5. Bram et al. does not teach what particular kinds of Fc fragments may be used in the fusion.

6. Bram et al. cannot properly inherently anticipate the claimed subject matter because Bram et al. does not teach the group of soluble receptors encompassed by the instant claims or does it disclose ztnf4 as a ligand for the receptors. Bram et al. does nothing more than assume that a ligand exists for this receptor and such an assumption is not a proper basis for a finding of anticipation.

7. Bram et al. disclose that the role of the ligand for inhibiting lymphocyte proliferation, the identity of the TACI protein is unknown and under law this admitted likelihood cannot serve as basis for inherent anticipation (*In re Rijckaert)*.

8. Only the claimed subject matter and not every statement set out in the '102 patent is presumed to be valid under 35 U.S.C. 282. Because the '102 patent does not claim the method of

the present invention, such statements are not entitled to presumptions of validity especially since the reference only speaks in terms of likelihood of a claimed result.

9. Presta does not remedy the deficiencies of the Bram reference.

Applicant's arguments have been fully considered and deemed non-persuasive.

Points 1-8 are addressed above. With regard to Point 9, Zntf4 is a member of the tumor necrosis factor (TNF) superfamily. Ztnf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Ztnf4 is a ligand for TACI and is also known in the art as BLyS, neutrokine α, BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see page 24, lines 24-26). Moreover, Bram et al. disclose that the "subunits" of the construct (i.e. TACI and the Fc domain of the Ig) can be linked by peptide bonds (see page 20, line 1). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular domain (see page 18, lines 27-30). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity (see page 8, lines 1-6). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit B cell proliferation, even though its identity is not known since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. hence Applicant's

argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that said composition binds BLyS. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand).

Finally, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 105-106 and 110-111, Bram et al. anticipates this limitation since their disclosed fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Bram et al. differs from the claimed invention in that they do not disclose the specific use of 1gG1 heavy chains in fusion proteins.

Presta et al. disclose methods of making fusion proteins comprising the Fc portion of an immunoglobulin (including IgG1)[see column 5, lines 48-55]. Presta et al. further disclose that the Fc portions of the various immunoglobulins have an increased circulatory half-life (see abstract and column 11, lines 63-65). Presta et al. teach that the Fc portions of the various immunoglobulins can be used interchangeably (see column 7, lines 3-45)

It would have been obvious for one of skill in the art at the time of the invention to modify the teachings of Bram et al. to include the teachings of Presta et al. because it is within the skill of the art to modify B cell activity (i.e. reduce B cell proliferation) by administering TACI receptor fusions comprising the Fc portion of an immunoglobulin, and because Presta et

al. teach it is within the skill in the art to construct and use fusion proteins comprising the Fc portion of IgG1. One would have been motivated to do so in order to achieve the expected result of generating TACI/Fc fusions functional in the methods disclosed by Bram et al. that have the increased circulatory half-life as disclosed by Presta et al.

Based on the state of the art and the teachings of the cited art, and absent of any evidence to the contrary, there would have been a reasonable expectation of success in combining the disclosure of Bram et al. with that of Presta et al. to obtain TACI/IgG1 Fc fusion proteins that are functional in the methods taught by Bram et al.

The rejection of claims 89 and 102-111 under 35 U.S.C. 103(a) as being unpatentable over Bram et al. (U.S. Patent 5,969,102 – IDS-5), as cited above, in view of Presta et al. (U.S. Patent 5,739,277) is maintained for reasons of record.

Applicant argues:

1. Bram et al. presents no data showing how a construct such as those described in the present application can be made. or any data demonstrating that said construct would work to inhibit B cell activity.

2. Bram et al. does not show specifically describe all the receptors of the present claims or identify ztnf4 or any other ligand.

3. Bram et al. does not provide data showing that the extracellular domain of any ztnf4 receptor will maintain its ability to bind ztnf4 absent the transmembrane and intracellular domains of the receptor.

4. Bram et al. does not show that the extracellular domain of TACI will bind to any ligand, let alone ztnf4 when fused to an Fc domain of an antibody.

5. Bram et al. does not teach what particular kinds of Fc fragments may be used in the fusion.

6. Bram et al. cannot properly inherently anticipate the claimed subject matter because Bram et al. does not teach the group of soluble receptors encompassed by the instant claims or does it disclose ztnf4 as a ligand for the receptors. Bram et al. does nothing more than assume that a ligand exists for this receptor and such an assumption is not a proper basis for a finding of anticipation.

7. Bram et al. disclose that the role of the ligand for inhibiting lymphocyte proliferation, the identity of the TACI protein is unknown and under law this admitted likelihood cannot serve as basis for inherent anticipation (*In re Rijckaert)*.

8. Only the claimed subject matter and not every statement set out in the '102 patent is presumed to be valid under 35 U.S.C. 282. Because the '102 patent does not claim the method of the present invention, such statements are not entitled to presumptions of validity especially since the reference only speaks in terms of likelihood of a claimed result.

9. Presta does not remedy the deficiencies of the Bram reference.

Applicant's arguments have been fully considered and deemed non-persuasive.

Points 1-8 are addressed above. With regard to Point 9, Zntf4 is a member of the tumor necrosis factor (TNF) superfamily. Ztnf4 stimulates proliferation of, and immunoglobulin production by, B cells. Moreover, Ztnf4 is a ligand for TACI and is also known in the art as BLyS, neutrokine α, BAFF, TALL-1 and THANK.

Bram et al. disclose methods of using genetically engineered constructs to regulate B-cell activity through its interaction with cellular receptor ligands. Said constructs can consist of the extracellular domain of the TACI receptor fused to the Fc domain of an immunoglobulin (see column 17, lines 16-18). Moreover, Bram et al. disclose that the "subunits" of the construct (i.e. TACI and the Fc domain of the Ig) can be linked by peptide bonds (see column 13, line 64). Bram et al. further disclose that said extracellular domain has the amino acid sequence corresponding to about residue 1 to about residue 166 of the consensus sequence of TACI and that the ligand binding region is a sub-fragment of the extracellular domain (see column 13, lines 7-12). Said constructs (fusion proteins) intercept the normal endogenous ligands (i.e. ztnf4) that serve to cross-link and activate the TACI proteins on the surface of cells thus inhibiting the ligand's activity (see column 5, lines 45-53). Consequently, by utilizing the methods and materials disclosed by Bram et al., one would necessarily inhibit B cell proliferation, even though its identity is not known since ztnf4 is an **endogenous ligand of TACI**. One does not need to know the identity of the TACI ligand in order to practice the method disclosed by Bram et al. hence Applicant's argument that the identification of the ztnf4 ligand would require undue experimentation is not germane. The instant claims only require that the TACI fusion protein be administered to an individual in order to inhibit B cell proliferation and that said composition binds BLyS. Bram et al. disclose the administration of the same the compositions for the expressed purpose of inhibiting B cell proliferation (which is a ztnf4 activity). Moreover, since the fusion proteins disclosed by Bram et al. are identical to those of the instant invention, said fusion proteins would possess all of the same properties as those of the instant invention (including the ability to bind the ztnf4 ligand).

Finally, with regard to the limitation "proteins comprising one or more polypeptide fusions" recited in claims 105-106 and 110-111, Bram et al. anticipates this limitation since their disclosed

fusion protein comprise one polypeptide fusion (i.e. the TACI-Fc fusion protein constitutes a single polypeptide fusion).

Bram et al. differs from the claimed invention in that they do not disclose the specific use of 1gG1 heavy chains in fusion proteins.

Presta et al. disclose methods of making fusion proteins comprising the Fc portion of an immunoglobulin (including IgG1)[see column 5, lines 48-55]. Presta et al. further disclose that the Fc portions of the various immunoglobulins have an increased circulatory half-life (see abstract and column 11, lines 63-65). Presta et al. teach that the Fc portions of the various immunoglobulins can be used interchangeably (see column 7, lines 3-45)

It would have been obvious for one of skill in the art at the time of the invention to modify the teachings of Bram et al. to include the teachings of Presta et al. because it is within the skill of the art to modify B cell activity (i.e. reduce B cell proliferation) by administering TACI receptor fusions comprising the Fc portion of an immunoglobulin, and because Presta et al. teach it is within the skill in the art to construct and use fusion proteins comprising the Fc portion of IgG1. One would have been motivated to do so in order to achieve the expected result of generating TACI/Fc fusions functional in the methods disclosed by Bram et al. that have the increased circulatory half-life as disclosed by Presta et al.

Based on the state of the art and the teachings of the cited art, and absent of any evidence to the contrary, there would have been a reasonable expectation of success in combining the disclosure of Bram et al. with that of Presta et al. to obtain TACI/IgG1 Fc fusion proteins that are functional in the methods taught by Bram et al.

35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 89 and 102-111 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record.

Applicant argues:

1. The claimed soluble receptors have been characterized as to their amino acid sequences and by certain common features (i.e. that ability to bind ztnf4). Moreover, the specification provides sufficient written description of changes that can be made in the receptors to support the claims to the genus of soluble receptors.

2. The reference to vast genus of soluble forms of ztnf4 is not understood since Applicant has identified 3 receptors that bind ztnf4 and have characterized the structural features of said receptors.

3. Any receptor that binds ztnf4 would inhibit B cell proliferation because they bind circulating ztnf4 and thus make it unavailable to bind B cell surface receptors.

Applicant's arguments have been fully considered and deemed non-persuasive.

With regard to Points 1 and 2, while Applicant has provided the amino acid sequences of 3 receptors, the domain(s) required for ztnf4 binding have not been provided. Consequently, the

specific structure of the claimed receptors has not been adequately described. Moreover, the disclosure of 3 specific species is insufficient to adequately describe the claimed genus.

With regard to Point 3, while Applicant is correct that the binding of ztnf4 in itself is predictive of whether a given receptor will inhibit B cell proliferation, it does not provide any indication as to what binding domains are required.

As outlined previously, the instant claims are drawn to a vast genus of **soluble forms of ztnf4 receptors**. To fulfill the written description requirements set forth under 35 USC § 112, first paragraph, the specification must describe at least a substantial number of the members of the claimed genus, or alternatively describe a representative member of the claimed genus, which shares a particularly defining feature common to at least a substantial number of the members of the claimed genus, which would enable the skilled artisan to immediately recognize and distinguish its members from others, so as to reasonably convey to the skilled artisan that Applicant has possession of the claimed invention. To adequately describe the genus of soluble forms of ztnf4 receptors, Applicant must adequately describe not only what constitutes a soluble ztnf4 receptor but also what constitutes the ztnf4 ligand. However, the specification does not disclose distinguishing and identifying features of a representative number of members of the genus of soluble ztnf4 receptors to which the claims are drawn, such as a correlation between the structure of the receptors and its recited function (i.e. inhibiting B-cell proliferation and binding ztnf4), so that the skilled artisan could immediately envision, or recognize at least a substantial number of members of the claimed genus. The claims are drawn to the use of any soluble protein comprising a sequence substantially identical to the ztnf4 receptor in a method for inhibiting B lymphocyte proliferation. The specification discloses that three polypeptides, BR43x2, TACI and

BCMA are disclosed to be able to bind ztnf4. **However, the specification does not place any structure, chemical or functional limitations on the variants of ztnf4 receptors. The recitation of " ztnf4 receptor" does not convey a common structure or function.** The scope of the claims includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members are permitted (e.g. TACI and BCMA). Moreover, the specification and the claims do not provide any guidance on the structure of the polypeptide and what changes can or cannot be made and retain the recited function. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure and the claims. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general guidance is needed. Since the disclosure fails to describe the common attributes or structural characteristics that identify members of the genus, and because the genus is highly variant, the function of the binding of ztnf4 alone is insufficient to describe the genus of "soluble ztnf4 receptor" polypeptides of that function equivalently. One of skill in the art would reasonable conclude that the disclosure of three sequences: SEQ ID NO:6 (TACI), SEQ ID NO:8 (BCMA) and SEQ ID NO:4 (BR43x2), fails to provide a representative number of species of soluble ztnf4 receptors to describe the claimed genus.

> MPEP § 2163.02 states, "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed' ". The courts have decided:
>
> The purpose of the "written description" requirement is broader than to merely explain how to "make and use"; the applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*

See *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Federal Circuit, 1991). Furthermore, the written description provision of 35 USC § 112 is severable from its enablement provision; and adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of more than one species within the genus. Therefore, because the art is unpredictable, in accordance with the *Guidelines*, the description of **soluble forms of ztnf4 receptors** is not deemed representative of the genus of polypeptides to which the claims refer.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Zeman whose telephone number is (571) 272-0866. The examiner can normally be reached on Monday- Thursday, 7am -5:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (571) 272-0864. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Robert A. Zeman
May 17, 2005

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